EM CASES SUMMARY

Episode 77 –Fever in the Returning Traveler

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Every year an increasing number of people travel abroad, and travelers to tropical destinations are often immunologically naïve to the regions they're going to. It's very common for travelers to get sick. In fact, about 2/3 of travelers get sick while they're traveling or soon after their return, and somewhere between 3 and 19% of travelers to developing countries will develop a fever.

Fever in the returning traveler is usually *not* caused by a dangerous tropical disease. These patients are much more likely to have typical viral illnesses as a cause for their fever. Nonetheless, all patients who return from traveling to a tropical destination with a fever require consideration of the common deadly tropical diseases: Malaria, Dengue and Typhoid fever.

Case 1 General approach to fever in the returning traveler

A 60 year-old male, presents with a fever to your ED. He recently returned from India, where he spent 3 weeks visiting relatives. He has no significant past medical history. Immunizations are up to date. He did id not receive any travel immunizations or malaria prophylaxis. The fever started 2 days ago, and is associated with cough and chills. In the ED his vital signs are: Temp 38.4°C, BP 135/85, HR 120 bpm, RR 22 and O2 saturation 94% on RA.

Key historical elements for fever in the returning traveler

While it seems obvious here, one of the common errors that emergency providers make in assessing fever is simply forgetting to ask a travel history and thus missing the deadly tropical disease diagnosis that has a vague presentation.

Ask about travel in **every** patient who presents with fever
The following areas are important to ask about in fever in the returning traveler:

Host Factors: past medical history, previous infections, diabetes, pregnancy, immunosuppression

Pre-travel Preparation: immunizations, malaria prophylaxis (type and compliance)

Specific Travel Itinerary: dates of travel, season of travel, destinations visited (regions, urban, rural), reason for travel, transportation

Exposure History: high-risk foods (local water, street food, uncooked meat), animal/insect exposure, bites, fresh water activities, blood and body fluid exposures (including sexual encounters, tattoos, IV drug use), sick contacts, health of fellow travelers

Physical Exam Features

While many features of the common deadly tropical diseases are vague, examination should include particular attention to the following:

- Vital signs (paradoxical bradycardia is sometimes seen in Typhoid fever)
- Neurologic Exam: mental status, meningismus
- Dermatologic Exam: skin lesions (rose spots of Typhoid fever, "islands of white in a sea of red" Dengue rash, eschar associated with tick bites of Rickettsia), petechiae, jaundice
- GI: hepatospenomegaly

Investigations to consider for fever in the returning traveler

Consider the following investigations for fever in the returning traveler:

- CBC & diff (look for anemia, lymphopenia, thrombocytopenia), electrolytes, creatinine, glucose, liver enzymes, bilirubin, and amylase
- Liver enzymes: look for a pattern of AST/ALT elevation (viral hepatitis, malaria)
- Blood cultures x 2
- Malaria Screen: thick and thin smears are required **every 12 hours** until there are **three negative smears**. Three negative smears are required to rule out Malaria as parasitemia is cyclical.
- Dengue serology

All patients returning from a Malaria endemic area with fever require 3 sets of thick and thin smears 12 hours apart to rule out malaria

Case 2 Malaria

A 35 year-old male presents to the ED with multiple seizures. Initial glucose is 2.1. He receives 2 amps of D50W and 2mg of IV lorazepam. After 2 more doses of lorazepam the seizures stop. Vital signs are: Temp 40.1°C, BP 78/43, HR 112 bpm, RR 34, O2 saturation 89% on a NRB. On exam, he is pale and diaphoretic. He has a decreased LOC, not following commands, but localizes to painful stimuli. Youhear bilateral crackles on respiratory exam and palpate diffuse abdominal tenderness with no peritoneal signs. He has no rash, no neck stiffness, and no meningismus. Collateral history reveals that he had recently been traveling to South Asia.

Q: **What is your differential diagnosis for this patient at this point?**

A: There is a wide differential diagnosis in this case, and we must consider illnesses that were pre-existing or pre-dated the travel. Important deadly diagnoses to consider are:

- Brain abscess
- HSV encephalitis
- Meningitis
- Severe malaria complicated by cerebral malaria
- Dengue shock syndrome

The clinical presentation of malaria

Fever is very common; 90% of patients will have or describe a fever. The fever may be the classic cyclic fever described with malaria that recurs every 2-3 days, or it may be continuous. The 'classic triad' in Malaria, like all 'classic triads' is nonspecific and insensitive. The 'classic triad' is fever, splenomegaly, and thrombocytopenia. Besides fever, the remainder of the presentation is fairly nonspecific. Symptoms like headache, cough, and GI symptoms are vague and can mimic other febrile illnesses such as influenza.

Patients with malaria will usually present with headaches, fever, myalgias and joint pain. They may have nausea, vomiting and diarrhea. Don't be fooled into making the definitive diagnosis of traveler's diarrhea if the patient presents with fever and diarrhea - they may have Malaria. More severe cases usually are jaundiced. The fever may be the classic cyclic fever described with malaria that recurs every 2-3 days, or it may be continuous. So, patients with Malaria may present to the ED without a measurable fever due to the cyclical nature of Malaria, however the fever is not cyclical in all patients with Malaria.

Species of Malaria to know about

Malaria can be caused by six known species of Plasmodium and is spread by the Anopheles mosquito. This mosquito

bites at night; thus, people who sleep in screened or air-conditioned rooms have a lower risk of contracting the disease.

P. falciparum is the species most likely to cause severe Malaria and death. Any cases of suspected Malaria should be considered to be *P. falciparum* until proven otherwise.

1. *P. knowlesi* has recently emerged in southeast Asian countries, and can cause severe and fatal infection. This should be treated similarly to *P. falciparum*.
2. *P.vivax, P. malariae, P. ovale* are other forms of Malaria that are less severe.

P. knowlesi is usually misdiagnosed as the less aggressive *P. malariae*, as the two are identical under microscopy. So any patient from Asia with a high parasitemia should be considered to have *P. knowlesi* until proven otherwise.

The significance of parasitemia level in Malaria

A parasite load of > 5% parasitized RBCs indicated severe malaria. While a high parasite load is fairly specific for severe Malaria and hence trigger a consideration for immediate IV anti-malarial medication, the parasite load may change over time and so patients who are found to have, no parasite load or a low parasite load should still be considered for empiric treatment with anti-malarials, as the subsequent smears may show increasing parasite loads. Do *not* rely on a single smear to rule out Malaria. The first smear is negative in 10% of patients because of fluctuating levels of parasitemia.

Pitfall: It is important to realize that interpretation of the Malaria thick and thin smears are highly dependent on the experience of the reader in the lab. It is not uncommon for the the species of Malaria to be misidentified as well as the parasite load be miscalculated. A common pitfall is not treating a patient who's smears show a less severe species with a low parasite load. All patients who present with severe malaria clinically should be presumed to have P. falciparum or P. knowlesi and treated with IV anti-malarials immediately, while less severe cases should still be considered for oral therapy and adminision even when a less severe species is identified in the smear with a low parasite load.

Disposition for Malaria

While there are no clear guidelines on disposition for patients with suspected Malaria, our experts recommend that all children and most adults with suspected Malaria should be considered for hospital admission as initial smears can be misleading, response to therapy is highly variable, and patients can rapidly deteriorate.

Common Pitfalls in the Management of Malaria

1. Failure to recognize travel as an element of the history.
2. Assuming that a patient who returns from a region known to have Malaria many months later cannot have Malaria. Malaria can have an incubation period of up to 12 months.
3. Assuming that if the patient is afebrile in the ED or doesn't have the typical cyclical fever of Malaria, they do not have Malaria.
4. Assuming that the chemoprophylaxis taken is the correct regimen, that the patient was compliant, or that chemoprophylaxis rules out Malaria.
5. Ruling out Malaria because the patient does not have the classic triad of fever, splenomegaly, and thrombocytopenia.
6. Relying on a single smear to rule out Malaria. The first smear is negative in 10% of patients because of fluctuating levels of parasitemia. In highly suspicious cases, failure to detect parasitemia is not an indication to withhold therapy. If there is a clinical suspicion of Malaria, repeat smears **every 12 hours** until there are **three negative smears** to rule out Malaria.
7. Misinterpretation of the smear by an inexperienced lab technician. *P. knowlesi* is usually misdiagnosed as the less aggressive *P. malariae*, as the two are identical under microscopy. Any patient from Asia with a high parasitemia should be considered to have *P. knowlesi* until proven otherwise.
8. Delaying treatment for suspected Malaria. A delay in treating *P. falciparum* > 6 hours is associated with worse outcomes. Do not delay treatment while awaiting lab confirmation.

[The CDC has an algorithm](#) to help you manage malaria.

Case 3 Typhoid Fever

A 21 year-old female presents to your ED with fever and chills for 10 days. She complains of fatigue, headache, malaise and crampy abdominal pain. She is more constipated than usual. She has no past medical history. She has recently traveled to Peru. Her vital signs are: Temp 38.2°C, BP 115/60, HR 43 bpm, Oxygen saturation 98%. On exam, appears well. Her GCS is 15 and her neck is supple. Her abdomen is slightly distended, with mild diffuse tenderness, but no peritoneal signs. There is no rash. All immunizations are up to date. In Peru, she stayed in homes and mostly urban areas, but also went hiking. She took malaria prophylaxis before and after the trip, but may have missed 1-2 doses. Her CBC is normal, she has mildly elevated liver enzymes. The blood culture comes back later positive for Salmonella Typhi.

Historical clues in Typhoid Fever

Relative bradycardia is often described in Typhoid Fever, however, like many of the signs of Typhoid Fever, relative bradycardia is nonspecific and insensitive for the diagnosis. While many patients with Typhoid Fever suffer from diarrhea, constipation can be seen in 40-50% of patients. Look for *rose spots* on the trunk and extremities - salmon-colored, blanching, maculopapules usually 1-4 cm wide and fewer than 5 in number which generally resolve within 2-5 days.
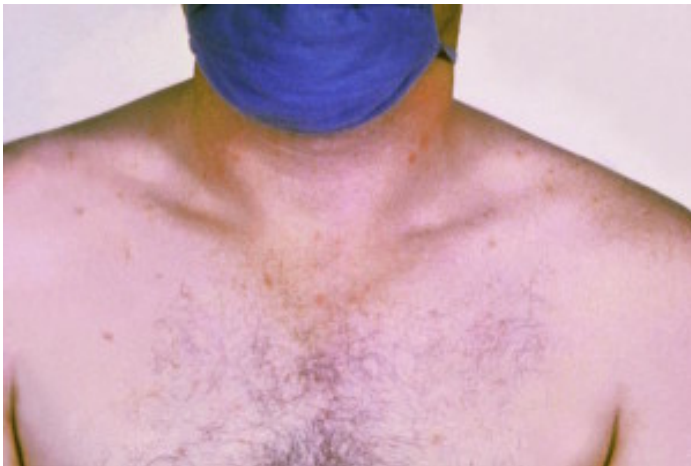
Rose spots of Typhoid Fever

The presentation can be divided into 3 weeks:

Week 1: diffuse abdominal pain and tenderness, constipation, dry cough, frontal headache, delirium, and an increasingly stuporous malaise

Week 2: *Rose spots,* progression of GI symptoms with abdominal distension, relative bradycardia

Week 3: weight loss, conjunctival injection, tachypnea, thready plulse, crackles over the lung bases, '*pea soup*' diarrhea, apathy, confusion, and even psychosis, peritonitis

Diagnosis of Typhoid Fever

Positive blood cultures for *Salmonella Typhi*. Gram negative bacilli are seen on gram stain. These results typically will not be available to the ED physician, so in the ED the diagnosis is usually presumptive based on clinical features.
Salmonella Typhi can also grow in urine and stool cultures, but these are less sensitive than blood cultures.

Treatment of Typhoid Fever

Local resistance patterns will dictate antibiotic choice. Consult the [CDC recommendations on Typhoid Fever](#)

Case 4 Dengue Fever

A 30 year-old female, returned from the Dominican Republic one week ago. She presents to the ED with a 3 day history of fever, headache, myalgias, and a petechial rash on her extremities. She is otherwise healthy. Immunizations are up to date. She received malaria prophylaxis. Her vital signs are: Temp 38.4°C, HR 120 bpm, RR 22, O2 saturation 94% on RA and normal BP. She has no signs of meningismus. Lab results includ WBC 3.2, platelts 80, and malaria smears x 2 are negative. Your differential diagnosis includes Malaria, Typhoid Fever and Dengue Fever.

Transmission of Dengue Fever

Dengue, or *breakbone fever*, is viral hemorrhagic fever that is transmitted by mosquitos and carries a high morbidity and mortality. There is a wide breadth of presentations, making this a difficult diagnosis. The incubation period is 3-14 days, with most patients presenting within the first week. Only some patients with Dengue present with the classic *saddle back fever,* a bimodal fever that persists for 3 days, resolves, and peaks again in 1-2 days.

The **WHO definition of Dengue** includes:

1. Fever
2. Two or more of:
   o Rash - petechia or "islands of white in a sea of red" (see image)
   o Arthralgias
   o Nausea/Vomiting
   o Positive tourniquet test (inflate BP cuff and leave it inflated for 5 minutes, on deflation, look distally for petechiae).
   o Leukopenia

"Islands of white in a sea of red" rash seen in Dengue Fever

Differentiating Dengue from Chikungunya

Dengue and Chikungunya are similar diseases; they are both acute febrile illnesses associated with exposure to mosquitos in appropriate parts of the world that usually present with headache and myalgias/arthralgias. As such, both diseases should be worked-up in patients returning from endemic areas. However, Dengue can lead to severe manifestations such as Dengue Hemorrhagic Fever, or Dengue Shock Syndrome, which is not seen in Chikungunya. The arthralgias in Chikungunya can lead to arthritis lasting for several months after the initial illness.

Dengue Septic Shock

Dengue septic shock occurs as the patient defervesces and lasts two to three days. A massive plasma leak occurs, leading to pleural effusions, ascites and hypovolemic shock. Patients also develop thrombocytopenia and DIC with massive hemorrhage. Treatment is supportive with red cells and judicious fluids.

References

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